PATENT--NO FEE

07

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicant:

A. DAUGAN

Serial No.: 08/669,389

Filed: July 16, 1996

For: **TETRACYCLIC DERIVATIVES, PROCESS OF PREPARATION AND USE**

Attorney Docket No.:
27866/33751

Group Art Unit: 1201

Examiner: T. Ngo

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date:

June 1, 1998

James J. Napoli
Registration No. 32,361
Attorney for Applicant

TRANSMITTAL OF PRIORITY DOCUMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed is a certified copy of the priority document for the above-identified application:

Country: Great Britain
Serial No.: 9401090.7
Filing Date: January 21, 1994

This document is filed in response to the Notice of Allowability dated May 7, 1998, in which it was indicated that no certified copy of the priority document was received by the Patent Office.

Also enclosed is a copy of Form PCT/IB/304 showing that the above-identified priority document was received by the International Bureau of WIPO. It is applicant's understanding that a copy of the priority document then was forwarded to the U.S. Patent Office under Rule 17 of the PCT regulations when PCT/EP95/00183 was entered into the U.S. national phase.

It is submitted that applicant has now perfected his claim to the benefit of the filing date of GB 9401090.7, and that this priority date should appear on the patent that issues from the above-identified application.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN, MURRAY & BORUN

By 

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Chicago, Illinois
June 1, 1998

The Patent Office

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP9 1RH

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed

Dated 21 May 1998

For official use

THE PATENT OFFICE
21 JAN 1994
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25JAN94W002B6521 PAT 1 77 UC 25.00

9401090.7

Your reference
LC/1233CV

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

CHEMICAL COMPOUNDS

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
LABORATOIRES GLAXO S. A.

Country *(and State of incorporation, if appropriate)*
FRANCE

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

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75016 PARIS
FRANCE

UK postcode
(if applicable)

Country FRANCE

ADP number
(if known) 4275335001

RP.

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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Forenames

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UK postcode
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Country

ADP number
(if known)

3
An address for service in the United Kingdom must be supplied.

Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ ***Please give details below***

Agent's name
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Agent's address
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GLAXO HOUSE
BERKELEY AVENUE
GREENFORD, MIDDLESEX

Postcode UB6 ONN

Agent's ADP number

Forrester Ketley & Co
Forrester House
52 Bounds Green Road
London
N11 2EY.

9792T2004

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number
(if known)

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4 Reference number

4 Agent's or applicant's reference number *(if applicable)* LC/1233CV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

❑ number of earlier application or patent number

❑ filing date *(day month year)*

❑ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, or
- any applicant is a corporate body.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	1		
Claim(s)		Description	58
Abstract		Drawing(s)	

NG

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

9 Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed L Caffin Date 20/01/1994

L. Caffin — Agent for the Applicant *(day month year)*

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

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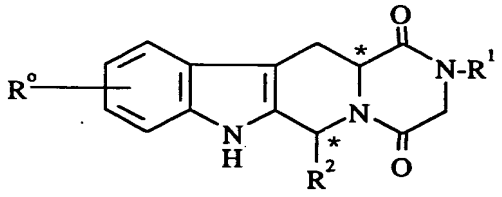
CHEMICAL COMPOUNDS

This invention relates to a series of tetracyclic derivatives, to processes for their preparation, pharmaceutical compositions containing them, and their use as therapeutic agents. In particular, the invention relates to tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders.

Thus, according to a first aspect, the present invention provides compounds of formula (I)

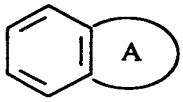


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

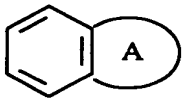
R^o represents hydrogen, halogen or C_{1-6} alkyl;

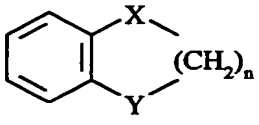
R^1 represents hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl; and

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

Within R^1 above, the term "aryl" as part of an arylC_{1-3}alkyl group means phenyl or phenyl substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6}alkyl and C_{1-6}alkoxy. The term "heteroaryl" as part of a heteroarylC_{1-3}alkyl group means thienyl, furyl or pyridyl each optionally substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6} alkyl and C_{1-6}alkoxy. The term "C_{3-8}cycloalkyl" as a group or part of a C_{3-8}cycloalkylC_{1-3}alkyl group means a monocyclic ring comprising three to

eight carbon atoms. Examples of suitable cycloalkyl rings include the C_{3-6}cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within R^2 above, optional benzene ring substituents are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, cyano, nitro and NR^aR^b where R^a and R^b are each hydrogen or C_{1-6}alkyl, or R^a may also represent C_{2-7}alkanoyl or C_{1-6}alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, C_{1-6}alkyl and C_{1-6}alkoxy. The bicyclic ring 

may, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene or benzofuran or 

(where n is an integer 1 or 2 and X and Y may each represent CH_2, O, S or NH).

In the above definitions, the term "alkyl" as a group or part of a group means a straight chain or, where available, a branched chain alkyl moiety. For example, it may represent a C_{1-4}alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. The term "haloC_{1-6}alkyl" means an alkyl group as defined above comprising one to six carbon atoms substituted at one or more carbon atoms by one or more (e.g. 1, 2 or 3) halogen atoms. Similarly, a haloC_{1-6}alkoxy group is a haloC_{1-6}alkyl group as defined above linked to the R^2 benzene ring via an oxygen atom. Examples of haloC_{1-6}alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC_{1-6}alkoxy group is trifluoromethoxy. The term "C_{2-7}alkanoyl" means a C_{1-6}alkylcarbonyl group where the C_{1-6}alkyl portion is as defined above. An example of a suitable C_{2-7}alkanoyl group is the C_2alkanoyl group acetyl.

It will be appreciated that when R^o is a halogen atom or a C_{1-6}alkyl group this substituent may be sited at any available position on the phenyl portion of the tetracyclic ring. However, a particular site of attachment is the ring 10-position.

The compounds of formula (I) may contain two or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. In particular, in formula

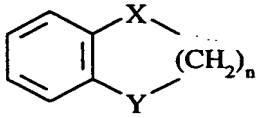
(I) above two ring chiral centres are denoted with asterisks. It is to be understood that the invention includes both mixtures and separate individual isomers of the compounds of formula (I).

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers thereof.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A particular group of compounds of the invention are those compounds of formula (I) in which R^o is hydrogen or halogen (e.g. fluorine), especially hydrogen.

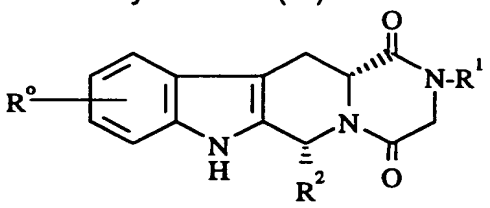
Another particular group of compounds of the invention are those compounds of formula (I) in which R^1 represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl,, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, pyridylC_{1-3}alkyl, furylC_{1-3}alkyl or optionally substituted benzyl. Within this particular group of compounds, examples of C_{1-4}alkyl groups are methyl, ethyl, n-propyl, i-propyl and n-butyl. Examples of C_{3-6}cycloalkylmethyl groups are cyclopropylmethyl and cyclohexylmethyl. Examples of optionally substituted, benzyl groups include benzyl and halobenzyl (e.g. fluorobenzyl).

A further particular group of compounds of the invention are those compounds of formula (I) in which R^2 represents an optionally substituted benzene, thiophene, furan, pyridine or naphthalene ring or an optionally substituted bicyclic ring 

(where n is 1 or 2 and X and Y are each CH_2 or O). Within this particular group of compounds, examples of substituted benzene groups are benzene substituted by one of halogen (e.g. chlorine), hydroxy, C_{1-3}alkyl (e.g. methyl, ethyl or i-propyl), C_{1-3}alkoxy (e.g. methoxy or ethoxy), halomethyl (e.g. trifluoromethyl), halomethoxy (e.g. trifluoromethoxy), cyano, nitro or NR^aR^b where R^a and R^b are each hydrogen

or methyl or R^a is acetyl; or benzene substituted by dihalo (e.g. dichloro) or by C_{1-3}alkoxy (e.g. methoxy) and one of halogen (e.g. chlorine) and hydroxy. An example of a substituted thiophene ring is a halo (e.g. bromo) substituent thiophene ring.

A preferred group of compounds of the invention are the cis isomers of formula (I) represented by formula (Ia)



(Ia)

and mixtures thereof with their cis optical enantiomers, including racemic mixtures, and salts and solvates (e.g. hydrates) of these compounds in which R^o is hydrogen or halogen (e.g. fluorine), especially hydrogen and R^1 and R^2 are as defined previously.

The pure isomers represented by formula (Ia), i.e. the 6R, 12aR isomers, are particularly preferred.

Within the above definitions R^1 may preferably represent C_{1-4}alkyl (e.g. methyl, ethyl, i-propyl and n-butyl), C_{3-6}cycloalkyl (e.g. cyclopentyl) or C_{3-6}cycloalkylmethyl (e.g. cyclopropylmethyl).

R^2 may preferably represent a substituted benzene ring such as benzene substituted by C_{1-3}alkoxy (e.g. methoxy) or by C_{1-3}alkoxy (e.g. methoxy) and halogen (e.g. chlorine), particularly 4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R^2 may preferably represent 3,4-methylenedioxyphenyl.

It is to be understood that the present invention covers all appropriate combinations of particular and preferred groupings hereinabove.

Particular individual compounds of the invention include:

cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

A specific compound of the invention is:
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The affinities of compounds of formula (I) for cGMP specific PDE (Phosphodiesterase type V) may be assessed by determination of their IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE V enzyme is isolated from bovine aorta, essentially by the method of Lugnier et al. in Biochem. Pharmacology 35, 1743 (1986) and assays are performed using a "one step" assay adapted from the method of Wells et al in Biochim. Biophys. Acta 384, 430 (1975). Results of these tests show that compounds of the present invention are potent inhibitors of cGMP specific PDE. Tests against other PDE enzymes using standard methodology also show that compounds of the invention are highly selective for the cGMP specific PDE enzyme.

Thus, as indicated above, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where inhibition of cGMP specific PDE is thought to be beneficial.

As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic, vasodilatory, natriuretic and diuretic activities as well as potentiation of the effects of

endothelium-derived relaxing factor (EDRF), nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT_1. The compounds of formula (I) therefore have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome).

It will be appreciated that references herein to treatment extend to prophylaxis as well as treatment of established conditions.

It will also be appreciated that references herein to 'a compound of formula (I)' embrace such a compound or a physiologically acceptable salt or solvate thereof, or a pharmaceutical composition containing either entity.

There is thus provided as a further aspect of the invention a compound of formula (I) for use in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

According to another aspect of the invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

In a further aspect, the invention provides a method of treating stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary

hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS) in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a compound with formula (I).

Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration. Oral administration is generally preferred.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I) will generally be in the range of from 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures

of PEG-8 and caprylic/capric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier.

A compound of formula (I) may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states. The invention thus provides, in another aspect, a combination of a compound of formula (I) together with another therapeutically active agent.

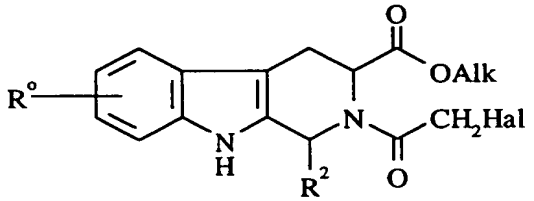
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a compound of formula (I) will be readily appreciated by those skilled in the art.

Compounds of formula (I) may be prepared by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below R^o, R^1 and R^2 are as defined in formula (I) above unless otherwise indicated.

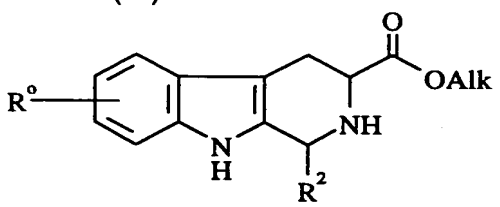
Thus, a process (A) for preparing a compound of formula (I) comprises treating a compound of formula (II)



(II)

(in which Alk represents C_{1-6}alkyl, e.g. methyl or ethyl and Hal is a halogen atom, e.g. chlorine) with a primary amine R^1NH_2 in a suitable solvent such as an alcohol (e.g. methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from 20°C to reflux (e.g. at about 50°C).

A compound of formula (II) may conveniently be prepared by treating a compound of formula (III)



(III)

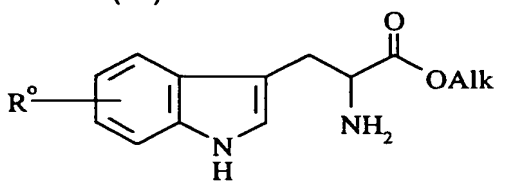
with a haloacetyl halide (e.g. chloroacetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). The reaction may conveniently be effected at a temperature of from -20°C to +20°C (e.g. at about 0°C).

A compound of formula (I) may also be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) may be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g. racemates) of either pairs of cis or trans isomers from the correspondong mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

A compound of formula (III) may conveniently be prepared from a tryptophan alkyl ester of formula (IV)



(IV)

(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) according to either of the following procedures (a) and (b). Procedure (b) is only suitable for preparing cis isomers of formula (III) and may be particularly suitable for preparing individual cis enantiomers of formula (III) from D- or L-tryptophan alkyl esters as appropriate.

Procedure (a)

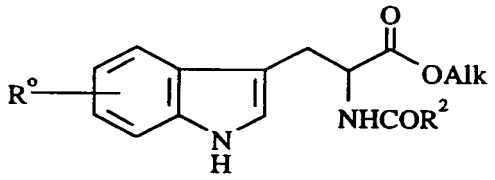
This comprises a Pictet-Spengler cyclisation between a compound of formula (IV) and an aldehyde R^2CHO. The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from -20°C to reflux to provide a compound of formula (III) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which may be either individual enantiomers or racemates of pairs of cis or trans isomers depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers may conveniently be separated from mixtures thereof by fractional crystallisation or by chromatography (e.g. flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers may be separated by chromatography (e.g. flash column chromatography) using appropriate eluents. An optically pure trans isomer may also be converted to an optically pure cis isomer using suitable epimerisation procedures. One such procedure comprises treating the trans isomer or a mixture (e.g. 1 : 1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from 0°C to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilising aqueous hydrogen chloride the desired cis isomer precipitates out as the hydrochloride salt which may then be isolated by filtration.

Procedure (b)

This comprises a four-step procedure from a compound of formula (IV) or a salt thereof (e.g. the hydrochloride salt). The procedure is particularly suitable for preparing a 1R, 3R isomer of formula (III) from a D-tryptophan alkyl ester of formula (IV) or a salt thereof (e.g. the hydrochloride salt). Thus, a first step (i) comprises treating a compound of formula (IV) with an acid halide R^2COHal

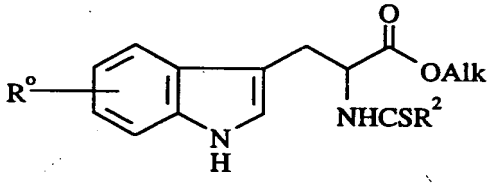
(where Hal is as previously defined) in the presence of a base, e.g. an organic base such as a trialkylamine (for example triethylamine), to provide a compound of formula (V)



(V)

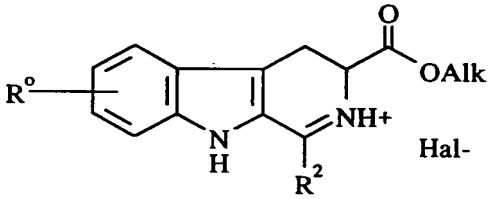
The reaction may be conveniently carried out in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) and at a temperature of from -20°C to +40°C.

Step (ii) comprises treating a compound of formula (V) with an agent to convert the amide group to a thioamide group. Suitable sulfurating agents are well-known in the art. Thus, for example, the reaction may conveniently be effected by treating (V) with Lawesson's reagent. This reaction may conveniently be carried out in a suitable solvent such as an ether (e.g. dimethoxyethane) or an aromatic hydrocarbon (e.g. toluene) at an elevated temperature such as from 40°C to 80°C to provide a compound of formula (VI)



(VI)

Step (iii) comprises treating a compound of formula (VI) with a suitable agent to provide a compound of formula (VII)



(VII)

(where Hal is a halogen atom, e.g. iodine). The reaction may conveniently be effected by treating (VI) with an alkylating agent such as a methyl halide (e.g. methyl iodide) or an acylating agent such as an acetyl halide (e.g. acetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) at an elevated temperature (e.g. under reflux).

In step (iv) the resulting iminium halide of formula (VII) may be treated with a reducing agent such as boron hydride, e.g. sodium borohydride, to provide the

desired compound of formula (III). The reduction may conveniently be effected at a low temperature, e.g. within the range of -100°C to 0°C, in a suitable solvent such as an alcohol (e.g. methanol).

Compounds of formula (I) may be converted to other compounds of formula (I). Thus, for example, when R^2 is a substituted benzene ring it may be necessary or desirable to prepare the suitably substituted compound of formula (I) subsequent to process (A) above. Examples of appropriate interconversions include nitro to amino by suitable reducing means (e.g. using a reducing agent such as $SnCl_2$) or amino to substituted amino such as acylamino or sulphonylamino using standard acylating or sulphonylating conditions.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

Thus, according to a further aspect of the invention, we provide a process for preparing a compound of formula (I) or a salt or solvate (e.g. hydrate) thereof which comprises process (A) followed by

i) an interconversion step; and/or either

ii) salt formation; or

iii) solvate (e.g. hydrate) formation.

Compounds of formula (III), except the compound in which R^o is hydrogen, R^1 is benzyl and R^2 is phenyl, are novel intermediates and represent a further aspect of the present invention.

The synthesis of the compounds of the invention and of the intermediates for use therein are illustrated by the following, non-limiting Examples. In the Examples section hereinafter the following abbreviations are used:

DMSO (dimethylsulphoxide), MeOH (methanol), EtOH (ethanol), DMF (dimethylformamide), EtOAc (ethyl acetate) and THF (tetrahydrofuran).

Intermediates 1 and 2

Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

To a stirred solution of racemic tryptophan methyl ester (13 g) and piperonal (9.7 g) in anhydrous CH_2Cl_2 (300 mL) cooled at 0°C was added dropwise trifluoroacetic acid (9 mL) and the solution was allowed to react at ambient temperature. After 4 days, the yellow solution was diluted with CH_2Cl_2 (100 mL), washed with a saturated aqueous solution of $NaHCO_3$, then with water and dried over Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (99/1) to give first Intermediate 1, the cis isomer (6.5 g) m.p. : 90-93°C followed by Intermediate 2, the trans isomer (6.4 g) m.p. : 170°C.

The following compounds were obtained in a similar manner :

Intermediates 3 and 4

Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 3, the cis isomer as white crystals m.p.: 142°C and Intermediate 4, the trans isomer as white crystals m.p.: 209-210°C.

Intermediate 5

Methyl 1,2,3,4-tetrahydro-1-(3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 3-methoxybenzaldehyde gave the title compound as white crystals m.p. : 146°C.

Intermediates 6 and 7

Methyl 1,2,3,4-tetrahydro-1-(4-ethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-ethoxybenzaldehyde gave Intermediate 6, the cis isomer as white crystals m.p. : 180°C and Intermediate 7, the trans isomer as white crystals m.p. : 196-198°C.

Intermediates 8 and 9

Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2,3-dihydrobenzo[b]furan-5- carboxaldehyde gave Intermediate 8, the cis isomer as white crystals m.p. : 106-109°C and Intermediate 9, the trans isomer as white crystals m.p. : 219-222°C.

Intermediates 10 and 11

Methyl 1,2,3,4-tetrahydro-1-(3,4-ethylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 1,4-benzodioxan-6-carboxaldehyde gave Intermediate 10, the cis isomer as white crystals m.p. : 104-106°C and Intermediate 11, the trans isomer as white crystals m.p. : 207-209°C.

Intermediate 12

Methyl 1,2,3,4-tetrahydro-1-(2-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2-chlorobenzaldehyde gave the title compound as white crystals m.p. : 154°C.

Intermediates 13 and 14

Methyl 1,2,3,4-tetrahydro-1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-chlorobenzaldehyde gave Intermediate 13, the cis isomer as white crystals m.p. : 208-209°C and Intermediate 14, the trans isomer as white crystals m.p. : 108-109°C.

Intermediates 15 and 16

Methyl 1,2,3,4-tetrahydro-1-(3,4-dichlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 3,4-dichlorobenzaldehyde gave Intermediate 15, the cis isomer as a white solid ^1H NMR ($CDCl_3$) δ (ppm) : 7.8-7 (m, 8H, H aromatic) ; 5.15 (brs, 1H, H-1) ; 3.9 - 3.8 (dd, 1H, H-3) 3.7 (s, 3H, CO_2CH_3) ; 3.2 - 3.1 (ddd, 1H, H-4) 2.9 (m, 1H, H-4) ; 2.4 (brs, 1H, NH) and Intermediate 16, the trans isomer as a white solid m.p. : 204°C.

Intermediate 17

Methyl 1,2,3,4-tetrahydro-1-(1,2,3,4-tetrahydro-6-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 1,2,3,4-tetrahydronaphthyl-6- carboxaldehyde gave the title compound as a white solid ^1H NMR ($CDCl_3$) δ (ppm) : 7.7-7(m, 8H, H aromatic) ; 5.2 (s, 1H, H-1) ; 4.0 (dd, 1H, H-3) ; 3.8 (s, 3H, CO_2CH_3) ; 3.2 (m, 1H, H-4) ; 3.0 (m, 1H, H-4) ; 2.7 (m, 4H, CH_2Ar) ; 1.7 (s, 4H, CH_2CH_2Ar).

Intermediates 18 and 19

Methyl 1,2,3,4-tetrahydro-1-(2-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2-naphthaldehyde gave Intermediate 18, the cis isomer as a white solid ^1H NMR ($CDCl_3$) δ (ppm) : 8-6.9 (m, 12H, H aromatic) ; 5.4 (s, 1H, H-1) ; 3.95 (dd, 1H, H-3) ; 3.7 (s, 3H, CO_2CH_3) 3.2 (ddd, 1H, H-4) ; 3 (m, 1H, H-4) ; 2.5 (brs, 1H, NH) and Intermediate 19, the trans isomer as a white solid (0.6 g) m.p. : 119°C.

Intermediates 20 and 21

Methyl 1,2,3,4-tetrahydro-1-(2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2-thiophenecarboxaldehyde gave Intermediate 20, the cis isomer as a pale yellow

solid m.p. : 134-137°C and Intermediate 21, the trans isomer as white crystals m.p. :169°C.

Intermediates 22 and 23

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 3-thiophenecarboxaldehyde gave Intermediate 22, the cis isomer as white crystals m.p. : 130°C and Intermediate 23, the trans isomer as white crystals m.p. :182-184°C.

Intermediates 24 and 25

Methyl 1,2,3,4-tetrahydro-1-(5-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 5-bromo-2-thiophenecarboxaldehyde gave Intermediate 24, the cis isomer as a cream solid m.p.: 130°C and Intermediate 25, the trans isomer as a cream solid m.p. : 205°C.

Intermediates 26 and 27

Methyl 1,2,3,4-tetrahydro-1-(4-bromo-2-thienyl))-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-bromo-2-thiophenecarboxaldehyde gave Intermediate 26, the cis isomer as a cream solid m.p.: 200°C and Intermediate 27, the trans isomer as a cream solid m.p. : 120°C.

Intermediate 28

Methyl 1,2,3,4-tetrahydro-1-(3-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 3-furaldehyde gave the title compound as a yellow solid m.p. : 130°C.

Intermediates 29 and 30

Ethyl 1,2,3,4-tetrahydro-1-(5-methyl-2-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 5-methylfurfural gave Intermediate 29, the cis isomer as a oily compound ^{1}H NMR ($CDCl_3$) δ (ppm) : 7.7 (brs, 1H, NH indole); 7.5 (d, 1H, H aromatic); 7.25-6.9 (m, 3H, H aromatic); 6.15 (d, 1H, H aromatic); 5.85 (m, 1H, H aromatic); 5.25 (brs, 1H, H-1); 4.2 (q, 2H, $CO_2C\underline{H}_2CH_3$); 3.8 (dd, 1H, H-3); 3.2 - 2.8 (m, 2H, H-4); 2.2 (s, 3H, CH_3); 1.25 (t, 3H, $CO_2CH_2C\underline{H}_3$) and Intermediate 30, the trans isomer as a cream solid m.p. : 152°C.

Intermediates 31 and 32

Ethyl 1,2,3,4-tetrahydro-1-(4-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and p-tolualdehyde gave Intermediate 31, the cis isomer as white crystals m.p. : 148°C and Intermediate 32, the trans isomer as white crystals m.p. : 180°C.

Intermediates 33 and 34

Methyl 1,2,3,4-tetrahydro-1-(3-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and m-tolualdehyde gave Intermediate 33, the cis isomer as white crystals ^{1}H NMR ($CDCl_3$) δ(ppm) : 7.6-7 (m, 9H, H aromatic); 5.2 (brs, 1H, H-1) ; 4-3.9 (dd, 1H, H-3) 3.8 (s, 3H, CO_2CH_3) ; 3.2 - 3.1 (ddd, 1H, H-4) 3 (m, 1H, H-4) ; 2.35 (s, 3H, CH_3) ; 1.7 (brs, 1H, NH) and Intermediate 34, the trans isomer as a white solid m.p. : 175°C.

Intermediates 35 and 36

Methyl 1,2,3,4-tetrahydro-1-(4-trifluoromethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-trifluoromethylbenzaldehyde gave Intermediate 35, the cis isomer as pale yellow crystals m.p. : 190°C and Intermediate 36, the trans isomer as pale yellow crystals m.p. : 203°C.

Intermediates 37 and 38
Ethyl 1,2,3,4-tetrahydro-1-(4-cyanophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers
The same method but starting from racemic tryptophan ethyl ester and 4-cyanobenzaldehyde gave Intermediate 37, the cis isomer as white crystals m.p. : 200°C and Intermediate 38, the trans isomer as white crystals m.p. : 156°C.

Intermediate 39
Methyl 1,2,3,4-tetrahydro-1-(4-hydroxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer
The same method but starting from racemic tryptophan ethyl ester and 4-hydroxybenzaldehyde gave the title compound as pale yellow crystals ^1H NMR (DMSO) δ(ppm) : 10.3 (s, 1H, NH-indole) 9.4 (s, 1H, OH) ; 7.8 - 7.5 (m, 8H, H aromatic) ; 5.1 (brs, 1H, H-1) ; 3.9 (m, 1H, H-3) ; 3.75 (s, 3H, CO_2CH_3) 3.1 (m, 1H, H-4) ; 2.8 (m, 1H, H-4).

Intermediate 40
Methyl 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer
The same method but starting from racemic tryptophan methyl ester and 3-hydroxy-4-methoxybenzaldehyde gave the title compound as a yellow solid m.p. : 140-148°C.

Intermediate 41
Methyl 1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer
The same method but starting from racemic tryptophan methyl ester and 4-hydroxy-3-methoxybenzaldehyde gave the title compound as a cream solid m.p. : 195°C.

Intermediate 42
Methyl 1,2,3,4-tetrahydro-1-(4-ethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers
The same method but starting from racemic tryptophan methyl ester and 4-ethylbenzaldehyde gave the cis and trans isomer of the title compound.

Cis isomer : white solid ^1H NMR ($CDCl_3$) δ(ppm) : 7.65-7.1 (m, 9H, H aromatic); 5.25 (brs, 1H, H-1) ; 4(dd, 1H, H-3) ; 3.9 (s, 3H, CO_2CH_3) ; 3.4 (ddd, 1H, H-4) ; 3.1 (m, 1H, H-4) ; 2.7 (q, 2H, CH_2CH_3) 1.4 (t, 3H, CH_2CH_3).
Trans isomer : white solid m.p. : 187°C.

Intermediates 43 and 44
Methyl 1,2,3,4-tetrahydro-1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-isopropylbenzaldehyde gave Intermediate 43, the cis isomer as a white solid ^1H NMR (DMSO) δ(ppm) : 10.15 (s, 1H, NH indole) ; 7.3-6.7 (m, 8H, H aromatic) ; 5 (brs, 1H, H-1) ; 3.6 (m, 1H, H-3) ; 3.5 (s, 3H, CO_2CH_3) ; 2.95-2.5 (m, 3H, H-4 + CH-$(Me)_2$) 2.4 (brs, 1H, NH) ; 1(d, 6H, 2xCH_3) and Intermediate 44, the trans isomer as a white solid m.p. : 189°C.

Intermediates 45 and 46
Ethyl 1,2,3,4-tetrahydro-1-(4-nitrophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-nitrobenzaldehyde gave Intermediate 45, the cis isomer as yellow crystals m.p. : 168°C and Intermediate 46, the trans isomer as yellow crystals m.p. : 195°C.

Intermediate 47
Ethyl 1,2,3,4-tetrahydro-1-(4-dimethylaminophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-dimethylaminobenzaldehyde gave the title compound as white crystals m.p. : 170°C.

Intermediates 48 and 49
Ethyl 1,2,3,4-tetrahydro-1-(3-pyridyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 3-pyridinecarboxaldehyde gave Intermediate 48, the cis isomer as pale yellow

crystals m.p. : 230-232°C and Intermediate 49, the trans isomer as white crystals m.p. : 210-214°C.

Intermediates 50 and 51

Methyl 1,2,3,4 tetrahydro-6-fluoro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic 5-fluoro-tryptophan methyl ester and piperonal gave Intermediate 50, the cis isomer as a cream solid m.p. :60°C and Intermediate 51, the trans isomer as a cream solid m.p. : 213°C.

Intermediates 52 and 53

Methyl 1,2,3,4-tetrahydro-6-fluoro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic 5-fluoro-tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 52, the cis isomer as a solid 1H NMR ($CDCl_3$) δ (ppm) : 7.4-6.8 (m, 8H, H aromatic) ; 5.15 (brs, 1H, H-1) ; 3.9 (dd, 1H, H-3) 3.8 (s, 3H, CO_2CH_3) ; 3.2-2.9 (m, 2H, H-4) and Intermediate 53, the trans isomer as a solid m.p. : 197°C.

Intermediates 54 and 55

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

To a stirred solution of D-tryptophan methyl ester (11 g) and piperonal (7.9 g) in anhydrous CH_2Cl_2 (400 mL) cooled at 0°C was added dropwise trifluoroacetic acid (7.7 mL) and the solution was allowed to react at ambient temperature. After 4 days, the yellow solution was diluted with CH_2Cl_2 (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$, then with water (3x200 mL) and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane/ethyl acetate (97/3) to give first Intermediate 54, the cis isomer (6.5 g) m.p. : 154°C followed by Intermediate 55, the trans isomer (8.4 g) m.p. : 188°C.

The following compounds were obtained in a similar manner :

Intermediate 56
(1S, 3S) Methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1R, 3S) methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer
The same method but starting from L-tryptophan methyl ester and piperonal gave the cis and trans isomers of the title compound.
Cis isomer : white crystals m.p. : 154°C.
Trans isomer : white crystals m.p. : 187-189°C.

Intermediates 57 and 58
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer
The same method but starting from D-tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 57, the cis isomer as white crystals m.p. : 124-125°C and Intermediate 58, trans isomer as white crystals m.p. : 219-222°C.

Intermediates 59 and 60
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl) 9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer
The same method, but starting from D-tryptophan methyl ester and 3-chloro-4-methoxybenzaldehyde gave Intermediate 59, the cis isomer isolated as the hydrochloride salt as white crystals m.p. : 200°C and Intermediate 60, the trans isomer as white crystals m.p. : 164°C.

Intermediates 61 and 62
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and

(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-(2,3-dihydrobenzo[b]furan))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method but starting from D-tryptophan methyl ester and 2,3-dihydrobenzo[b]furan-5-carboxaldehyde gave Intermediate 61, the cis isomer as white crystals m.p. : 282°C and Intermediate 62, the trans isomer as white crystals m.p. : 204°C.

Intermediates 63 and 64

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and

(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

The same method but starting from D-tryptophan methyl ester and indan-5-carboxaldehyde gave Intermediate 63, the cis isomer as white crystals m.p. : 130-131°C and Intermediate 64, the trans isomer as white crystals m.p. : 196°C.

Intermediate 65

Ethyl 1,2,3,4-tetrahydro-1-(4-trifluoromethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-trifluoromethoxybenzaldehyde gave cis and trans isomers of the title compound.

Cis isomer : white crystals m.p. : 88°C.

Trans isomer : white crystals m.p. : 152°C.

Intermediate 66

Methyl 1,2,3,4-tetrahydro-1-(5-methyl-2-thienyl)-9H-pyrido [3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 5-methyl-2-thiophenecarboxaldehyde gave the cis and trans isomers of the title compound.

Cis isomer : oily compound ^1H NMR ($CDCl_3$) δ (ppm) : 8.4 (brs, 1H, NH-indole); 7.7 - 6.6 (m, 6H, H aromatic); 5.5 (brs, 1H, H-1); 3.9 (dd, 1H, H-3); 3.85 (s, 3H, CO_2CH_3); 3.3 - 2.9 (m, 2H, H-4); 2.5 (s, 3H, CH_3).

Trans isomer : white crystals m.p. : 194°C.

Intermediates 67 and 68

(1S,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate and

(1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

To a stirred solution of D-tryptophan methyl ester (obtained by treating the corresponding hydrochloride salt in water with saturated aqueous $NaHCO_3$ solution and extraction with CH_2Cl_2) (25.7g) and piperonal (19.4g) in anhydrous dichloromethane (700ml) cooled to 0°C was added dropwise trifluoroacetic acid (18.1ml) and the solution was allowed to react at 4°C. After 5 days, the yellow solution was diluted with dichloromethane (500ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, then with water (3 x 500ml) until the pH was neutral and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to a volume of about 500ml. The trans-isomer, which crystallised, was filtered and the filtrate was reduced to 200ml. Another fraction of the trans-isomer crystallised. The fractions of trans-isomer were combined to give the (1S,3R) isomer, Intermediate 67, as white crystals (11.4g).

mp : 188°C

$[\alpha]_D^{20°}$ = +32.4° (c = 1.03, $CHCl_3$).

The filtrate containing mainly the cis-isomer was reduced to 100ml and isopropyl ether (200ml) was added. Upon cooling, the (1R,3R) isomer, Intermediate 68, crystallised as a white solid (17.4g).

mp : 154-155°C

$[\alpha]_D^{20°}$ = + 24.4° (c = 1.03, $CHCl_3$).

Intermediate 69

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

Intermediate 67 (5.0g) was dissolved in methanol (150ml). Hydrogen chloride was bubbled into the solution for several minutes at 0°C and the resulting yellow solution was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue was basified with a saturated aqueous solution of

$NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and purified by flash chromatography eluting with dichloromethane/methanol (99/1) to give the title compound (2.3g) corresponding to an authentic sample of Intermediate 68.

Method B

Intermediate 67 (25g) was heated in 1N hydrochloric acid (78.5ml) and water (400ml) at 60°C for 36 hours. From the initial pale yellow solution, a white solid precipitated. The mixture was then allowed to cool to 0°C and the solid filtered. The solid was then washed with diisopropyl ether (3 x 200ml) and dried to give the hydrochloride salt of the title compound (20g) as a white solid.

mp (dec.) : 209 - 212°C

Method C

A 1 : 1 mixture of the cis and trans isomers of Intermediates 54 and 55 (2g) was heated in 1N hydrochloric acid (6.8ml) and water (15ml) at 50°C for 72 hours. A similar work-up as described in Method B above gave the hydrochloride salt of the title compound (1.7g) as a white solid.

Intermediate 70

(R)-N^{α}-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

To a suspension of D-tryptophan methyl ester hydrochloride (10.2g) in anhydrous CH_2Cl_2 (150ml) cooled at 0°C was added dropwise triethylamine (12.3ml). To the resulting solution solid piperonyloyl chloride (8.16g) was added portionwise at the same temperature, and the mixture was stirred at room temperature for 2 h. The mixture was washed successively with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of $NaHCO_3$ and again with water. After drying over Na_2SO_4 and evaporation of the solvent under reduced presure, the resulting oil on trituration from hot cyclohexane afforded the title compound as a white solid (14.7g).

mp : 123-124°C

$[\alpha]_D^{20°}$ = - 84.4° (c = 1.04, $CHCl_3$).

Intermediate 71

(R)-N^{α}-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

A mixture of Intermediate 70 (14g) and Lawesson's reagent (9.28g) in dimethoxyethane (280ml) was heated at 60°C under N_2 for 16 hours with stirring. The reaction mixture was evaporated to dryness and the resulting oil was dissolved in ethyl acetate, then washed successively with an aqueous saturated solution of $NaHCO_3$ and water and dried over Na_2SO_4. The oily residue obtained after evaporation under reduced pressure gave, on trituration from cyclohexane, a yellow powder which was filtered and washed with cooled methanol to afford the title compound (9.74g).

mp : 129-130°C

$[\alpha]_D^{20°}$ = - 186.8° (c = 1.14, $CHCl_3$).

Intermediate 72

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of Intermediate 71 (9g) and methyl iodide (10ml) in anhydrous dichloromethane (200ml) was heated at reflux under an argon atmosphere with protection from light. After 24 hours, the solvent was removed under reduced pressure to give an orange oil which on trituration from hexane gave a solid which was washed with ether and used without further purification in the next step. This compound (13.11g) was dissolved in methanol (250ml) and the solution was cooled to -78°C. $NaBH_4$ (0.99g) was then added by portions and the mixture was stirred at the same temperature for 1 hour. The reaction was quenched by addition of acetone (10ml) and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and then with brine and dried over Na_2SO_4. After evaporation of the solvent, the orange oil gave on trituration from a hot mixture of diethyl ether/cyclohexane an orange powder which was recrystallised from diethyl ether/pentane to afford the title compound as a pale yellow solid (5.15g) corresponding to an authentic sample of Intermediate 68.

Intermediate 73

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

To a stirred solution of Intermediate 72 (9.7g) and $NaHCO_3$ (2.79g) in anhydrous $CHCl_3$ (200ml) was added dropwise chloroacetyl chloride (5.3ml) at 0°C under N_2. The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$ (100ml). Water (100ml) was then added dropwise with stirring to the mixture, followed by a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the oily compound obtained was crystallised from ether to give the title compound as a pale yellow solid (9.95g).

mp : 233°C

$[\alpha]_D^{20°} = -125.4°$ (c = 1.17, $CHCl_3$).

Method B

Chloroacetyl chloride (4ml) was added dropwide to a solution of Intermediate 72 (16.1g) and triethylamine (7ml) in anhydrous CH_2Cl_2 (200ml) at 0°C under N_2. The solution was stirred at 0°C for 30 minutes, then diluted with CH_2Cl_2 (300ml). The solution was washed with water (200ml), a saturated aqueous solution of $NaHCO_3$ (300ml) and brine (400ml). After drying over Na_2SO_4 and evaporation under reduced pressure, the resulting solid was washed with ether (300ml) to give the title compound as a pale yellow solid (18.3g).

Intermediate 74

Methyl 1,2,3,4-tetrahydro-6-methyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The cis and trans isomers of the title compound were prepared using the method described in Intermediate 1 but starting from racemic 5-methyl-tryptophan methyl ester and piperonal.

Cis isomer : yellow solid m.p. : 85°C.

Trans isomer : yellow solid m.p. : 185°C.

Example 1

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

a) To a stirred solution of intermediate 1 (2 g) and $NaHCO_3$ (0.6 g) in anhydrous $CHCl_3$ (40 mL) was added dropwise chloroacetyl chloride (1.1 mL) at 0°C.

The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$. Water (20 mL) was then added dropwise with stirring to the mixture, followed by a saturated solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, cis-methyl 1,2,3,4-tetrahydro-2-chloroacetyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was obtained as an oil which was crystallised from ether (2 g, m.p. : 215-218°C) and was used without further purification in the next step.

b) To a stirred suspension of the chloroacetyl intermediate (0.34 g) in MeOH (20 mL) was added at ambient temperature a solution of methylamine (33% in EtOH) (0.37 mL) and the resulting mixture was heated at 50°C under N_2 for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x30 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (99/1) and recrystallised from MeOH to give the title compound as white crystals (0.19 g) m.p. : 253-255°C.

Analysis for $C_{22}H_{19}N_3O_4$:
Calculated:C,67.86;H,4.92;N,10.79;
Found:C,67.53;H,4.99;N,10.62%.

The following compounds were obtained in a similar manner :

Example 2

Cis-2, 3, 6, 7, 12, 12a-hexahydro-2-butyl-10-fluoro-6-(4-methoxyphenyl)-pyrazino[2', 1' : 6,1]pyrido [3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 52 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 182°C.

Analysis for $C_{25}H_{26}FN_3O_3$ (0.1 H_2O):
Calculated : C, 68.67 ; H, 6.04 ; N, 9.61;
Found : C, 68.38 ; H, 6.11 ; N, 9.53%.

Example 3
Trans-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 2 gave, after recrystallisation from toluene, the title compound as white crystals m.p. : 301-303°C.
Analysis for $C_{22}H_{19}N_3O_4$:
Calculated: C,67.86;H,4.92;N,10.79;
Found:C,67.98;H,4.98;N,10.73%.

Example 4
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from ammonia and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 283-285°C.
Analysis for $C_{21}H_{17}N_3O_4$:
Calculated: C,67.19;H,4.56;N,11.19;
Found:C,67.04;H,4.49;N,11.10%.

Example 5
Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)-pyrazino[2',1' : 6,1]pyrido [3,4-b]indole-1,4-dione
The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 52 gave, after recrystallisation from ethanol/diisopropyl ether, the title compound as white crystals m.p. : 190°C.
Analysis for $C_{23}H_{19}F_4N_3O_3$:
Calculated : C, 59.87 ; H, 4.15 ; N, 9.11;
Found : C, 59.81 ; H, 4.18 ; N, 9.21%.

Example 6
Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 50 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 292°C.

Analysis for $C_{22}H_{18}FN_3O_4$:

Calculated : C, 64.86 ; H, 4.45 ; N, 10.31;

Found : C, 64.66 ; H, 4.60 ; N, 10.21%.

Example 7

(6R, 12aS)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6.1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the trans isomer of intermediate 56 gave, after recrystallisation from toluene, the title compound as white crystals m.p. :287-289°C.

Analysis for $C_{22}H_{19}N_3O_4$ (0.25 toluene):

Calculated : C, 69.16 ; H, 5.13 ; N, 10.19;

Found : C,69.09 ; H, 5.14 ; N, 10.19%.

$[\alpha]_D^{20°}$ = -293.4° (C=1.28; $CHCl_3$).

Example 8

(6S, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino [2', 1' : 6.1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 55 gave, after recrystallisation from toluene, the title compound as white crystals m.p. : 287°C.

Analysis for $C_{22}H_{19}N_3O_4$ (0.3 toluene):

Calculated : C, 69.41 ; H, 5.17 ; N, 10.08;

Found : C, 69.56 ; H,5.24 ; N, 10.08%.

$[\alpha]_D^{20°}$ = + 297.9° (C=1.21; $CHCl_3$).

Example 9

Cis-2, 3, 6, 7, 12, 12a-hexahydro-2-[2-(2-pyridyl)-ethyl]-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1'-6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2-(2-pyridyl)ethylamine and intermediate 1 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 218-222°C.
Analysis for $C_{28}H_{24}N_4O_4$:
Calculated : C, 69.99 ; H, 5.03 ; N, 11.66;
Found : C, 69.92 ; H, 5.16 ; N, 11.48%.

Example 10
Cis-2,3,6,7,12,12a-hexahydro-2-(2-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione
The same two step procedure but starting from 2-pyridylmethylamine and intermediate 1 gave, after recrystallisation from DMF/water, the title compound as cream crystals m.p : 285-286°C.
Analysis for $C_{27}H_{22}N_4O_4$ (0.4 H_2O):
Calculated : C, 68.46 ; H,4.85 ; N, 11.83;
Found : C, 68.58 ; H, 4.88 ; N, 11.90%.

Example 11
Cis-2,3,6,7,12,12a-hexahydro-2-(3-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione
The same two step procedure but starting from 3-pyridylmethylamine and intermediate 1 gave, after recrystallisation from CH_2Cl_2/MeOH, the title compound as cream crystals m.p. : 292-293°C.
Analysis : $C_{27}H_{22}N_4O_4$:
Calculated : C, 69.52 ; H, 4.75 ; N, 12.01;
Found : C, 69.27 ; H, 4.74 ; N, 11.37%.

Example 12
Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione
The same two step procedure but starting from 4-pyridylmethylamine and intermediate 1 gave, after recrystallisation from MeOH, the title compound as pale yellow crystals m.p. : 273-274°C.
Analysis for $C_{27}H_{22}N_4O_4$ (1.8 H_2O):
Calculated : C, 65.00 ; H, 5.17 ; N, 11.23;

Found : C, 65.11 ; H, 4.85 ; N, 11.07%.

Example 13

Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from ethylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 272-274°C.

Analysis for $C_{23}H_{21}N_3O_4$:

Calculated: C,68.47;H,5.25;N,10.42;

Found:C,68.52;H,5.35;N,10.53%.

Example 14

Cis-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 1 gave, after recrystallisation from EtOH, the title compound as white crystals m.p. : 303°C.

Analysis for $C_{23}H_{18}F_3N_3O_4$:

Calculated: C,60.40;H,3.97;N,9.19;

Found:C,60.43;H,4.15;N,9.16%.

Example 15

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-2-propyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from propylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 270-271°C.

Analysis for $C_{24}H_{23}N_3O_4$:

Calculated: C,69.05;H,5.55;N,10.07;

Found:C,69.22;H,5.50;N,9.80%.

Example 16

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 248-250°C.
Analysis for $C_{24}H_{23}N_3O_4$:
Calculated: C,69.05;H,5.55;N,10.07;
Found:C,68.86;H,5.66;N,10.21%.

Example 17
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from cyclopropylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 290-292°C.
Analysis for $C_{24}H_{21}N_3O_4$:
Calculated: C,69.39;H,5.10;N,10.11;
Found:C,69.11;H,5.20;N,9.94%.

Example 18
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from butylamine and intermediate 1 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 241-243°C.
Analysis for $C_{25}H_{25}N_3O_4$:
Calculated: C,69.59;H,5.84;N,9.74;
Found:C,69.77;H,5.82;N,9.81%.

Example 19
Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from butylamine and intermediate 2 gave, after recrystallisation from toluene, the title compound as white crystals m.p. : 243°C.
Analysis for $C_{25}H_{25}N_3O_4$:
Calculated: C,69.59;H,5.84;N,9.74;

Found:C,69.80;H,5.78;N,9.52%.

Example 20

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 217-218°C.

Analysis for $C_{25}H_{23}N_3O_4$:

Calculated: C,69.92;H,5.40;N,9.78;

Found:C,70.02;H,5.47;N,9.84%.

Example 21

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 1 gave, after recrystallisation from acetone, the title compound as white crystals m.p. : 270°C.

Analysis for $C_{26}H_{25}N_3O_4$:

Calculated: C,70.41;H,5.68;N,9.47;

Found:C,70.58;H,5.63;N,9.38%.

Example 22

Cis-2,3,6,7,12,12a-hexahydro-2-cyclohexyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclohexylamine and intermediate 1 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 268-269°C.

Analysis for $C_{27}H_{27}N_3O_4$:

Calculated: C,70.88;H,5.95;N,9.18;

Found:C,70.82;H,5.89;N,9.21%.

Example 23

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from benzylamine and intermediate 1 gave, after recrystallisation from dichloromethane/hexane, the title compound as white crystals m.p. : 285-287°C.
Analysis for $C_{28}H_{23}N_3O_4(1\ H_2O)$:
Calculated: C,69.55;H,5.21;N,8.69;
Found:C,69.30;H,5.06;N,8.48%.

Example 24
Cis-2,3,6,7,12,12a-hexahydro-2-(4-fluorobenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from 4-fluorobenzylamine and intermediate 1 gave, after recrystallisation from acetone, the title compound as white crystals m.p. : 281-283°C.
Analysis for $C_{28}H_{22}FN_3O_4$:
Calculated: C,69.56;H,4.59;F,3.93;N,8.69;
Found:C69.54;H,4.58;F,3.82;N,8.63%.

Example 25
Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 3 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 257-263°C.
Analysis for $C_{22}H_{21}N_3O_3$:
Calculated: C,70.38;H,5.64;N,11.19;
Found:C,70.11;H,5.55;N,11.15%.

Example 26
Trans-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 4 gave, after recrystallisation from diisopropyl ether, the title compound as white crystals m.p. : 225-228°C.
Analysis for $C_{22}H_{21}N_3O_3$:
Calculated: C,70.38;H,5.64;N,11.19;

Found:C,70.34;H,5.77;N,11.19%.

Example 27

Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from ethylamine and intermediate 3 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 245-255°C.

Analysis for $C_{23}H_{23}N_3O_3$:

Calculated: C,70.93;H,5.95;N,10.79;

Found:C,70.74;H,6.06;N,10.87%.

Example 28

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 3 gave, after recrystallisation from ethanol , the title compound as white crystals m.p. : 232°C.

Analysis for $C_{23}H_{20}F_3N_3O_3$:

Calculated: C,62.30;H,4.55;N,9.48;

Found:C,62.08;H,4.66;N,9.54%.

Example 29

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 3 gave, after recrystallisation from methanol,the title compound as white crystals m.p. : 157°C.

Analysis for $C_{25}H_{27}N_3O_3(0.5H_2O)$:

Calculated: C,70.40;H,6.62;N,9.85;

Found:C,70.25;H,6.60;N,9.83%.

Example 30

Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 4 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 212-214°C.

Analysis for $C_{25}H_{27}N_3O_3$:

Calculated: C,71.92;H,6.52;N,10.06;

Found:C,71.81;H,6.55;N,10.03%.

Example 31

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 3 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 180-185°C.

Analysis for $C_{25}H_{25}N_3O_3$ ($0.5H_2O$):

Calculated: C,70.74;H,6.17;N,9.90;

Found:C, 70.91 ; H, 6.16 ; N, 9.80%.

Example 32

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from benzylamine and intermediate 3 gave, after recrystallisation from acetone, the title compound as white crystals m.p. : 275-279°C.

Analysis for $C_{28}H_{25}N_3O_3$:

Calculated: C,74.48;H,5.58;N,9.31;

Found:C,74.53;H,5.60;N,9.20%.

Example 33

Cis-2,3,6,7,12,12a-hexahydro-6-(3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 5 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 267-269°C.

Analysis for $C_{22}H_{21}N_3O_3$:

Calculated: C,70.38;H,5.64;N,11.19;

Found:C,70.32;H,5.59;N,11.25%.

Example 34

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 6 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 247-248°C.

Analysis for $C_{23}H_{23}N_3O_3$:

Calculated: C,70.93.H,5.95;N,10.79;

Found:C,71.23;H,5.95;N,10.63%.

Example 35

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 6 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 160-162°C.

Analysis for $C_{26}H_{27}N_3O_3$:

Calculated: C,72.71;H,6.34;N,9.78;

Found:C,72.28;H,6.39;N,9.71%.

Example 36

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 8 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 292-294°C.

Analysis for $C_{23}H_{21}N_3O_3$:

Calculated: C,71.30;H,5.46;N,10.85;

Found:C,71.15;H,5.56;N,10.84%.

Example 37

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 8 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 165-166°C.
Analysis for $C_{26}H_{25}N_3O_3$:
Calculated: C,73.05;H,5.89;N,9.83;
Found:C,73.08;H,5.97;N,9.87%.

Example 38
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 10 gave, after recrystallisation from acetone, the title compound as white crystals m.p. : 303-305°C.
Analysis for $C_{23}H_{21}N_3O_4$:
Calculated: C,68.47;H,5.25;N,10.42;
Found:C,68.35;H,5.31;N,10.27%.

Example 39
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from cyclopropylmethylamine and intermediate 10 gave, after recrystallisation from dichloromethane/ether, the title compound as white crystals m.p. : 288-290°C.
Analysis for $C_{26}H_{25}N_3O_4$:
Calculated: C,70.41;H,5.68;N,9.47;
Found:C,70.15;H,5.62;N,9.30%.

Example 40
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from butylamine and intermediate 12 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 146°C.
Analysis for $C_{24}H_{24}ClN_3O_2(0.75\ H_2O)$:
Calculated: C,66.20;H,5.90;N,9.65;

Found:C,66.15;H,5.95;N,9.69%.

Example 41

Cis-2,3,6,7,12,12a-hexahydro-6-(4-chlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 13 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 274°C.

Analysis for $C_{21}H_{18}ClN_3O_2$ (0.25 H_2O):

Calculated: C,65.63;H,4.85;N,10.93;

Found:C,65.39;H,4.84;N,10.85%.

Example 42

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 13 gave, after recrystallisation from ethanol/water, the title compound as white crystals m.p. : 164-166°C.

Analysis for $C_{24}H_{24}ClN_3O_2$:

Calculated: C,68.32;H,5.73;Cl,8.40;N,9.96;

Found:C,68.48;H,5.64;Cl,8.37;N,9.99%.

Example 43

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-dichlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 15 gave, after recrystallisation from ethanol/DMF, the title compound as white crystals m.p. : >260°C.

Analysis for $C_{21}H_{17}Cl_2N_3O_2$ (0.5 H_2O):

Calculated: C,59.39;H,4.29;N,9.93;

Found:C,59.32;H,4.16;N,9.99%.

Example 44

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and cis-methyl 1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate[1] gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 243-245°C.

Analysis for $C_{24}H_{25}N_3O_2$:
Calculated: C,74.39;H,6.50;N,10.84;
Found:C,74.54;H,6.51;N,10.86%.

1. D. Soerens et al., J. Org. Chem. 44, 535 - 545 (1979).

Example 45
Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 193-195°C.

Analysis for $C_{27}H_{23}N_3O_2$:
Calculated: C,76.94;H,5.50;N,9.97;
Found:C,77.23;H,5.54;N,9.97%.

Example 46
Trans-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 284°C.

Analysis for $C_{27}H_{23}N_3O_2$:
Calculated: C,76.94;H,5.50;N,9.97;
Found:C,76.88;H,5.45;N,9.89%.

Example 47
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 17 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : >260°C.
Analysis for $C_{25}H_{25}N_3O_2$:
Calculated: C,75.16;H,6.31;N,10.52;
Found:C,74.93;H,6.43;N,10.63%.

Example 48
Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from isopropylamine and intermediate 17 gave, after recrystallisation from the title compound as off-white crystals m.p. : 244-246°C.
Analysis for $C_{27}H_{29}N_3O_2$ ($0.25H_2O$):
Calculated: C,75.06;H,6.88;N,9.73;
Found:C,75.00;H,6.83;N,9.69%.

Example 49
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(1,2,3,4-tetrahydro-6-naphthyl))-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from cyclopropylmethylamine and intermediate 17 gave, after recrystallisation from ethanol/pentane, the title compound as white crystals m.p. : 125°C.
Analysis for $C_{28}H_{29}N_3O_2$ ($0.25\ H_2O$):
Calculated: C,75.73;H,6.70;N,9.46;
Found:C,75.45;H,6.86;N,9.14%.

Example 50
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(2-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 18 gave, after recrystallisation from dichloromethane/methanol, the title compound as white crystals m.p. : >260°C.
Analysis for $C_{25}H_{21}N_3O_2$ ($0.25H_2O$):
Calculated: C,75.08;H,5.42;N,10.51;

Found:C,75.35;H,5.42;N,10.49%.

Example 51

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 20 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 226°C.

Analysis for $C_{22}H_{23}N_3O_2S$:

Calculated: C,67.15;H,5.89;N,10.68;

Found:C,67.39;H,5.88;N,10.77%.

Example 52

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as a cream powder m.p. : 258°C.

Analysis for $C_{19}H_{16}BrN_3O_2S$:

Calculated: C,53.03;H,3.75;N,9.76;

Found:C,53.01;H,3.78;N,9.69%.

Example 53

Cis-2,3,6,7,12,12a-hexahydro-6-(4-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 26 gave, after recrystallisation from ethanol, the title compound as white crystals mp. : 292°C.

Analysis for $C_{19}H_{16}BrN_3O_2S$ ($0.25H_2O$):

Calculated: C,52.48;H,3.82;N,9.66;

Found:C,52.46;H,3.81;N,9.60%.

Example 54

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 190°C.

Analysis for $C_{22}H_{20}BrN_3O_2S$:

Calculated: C,56.18;H,4.29;N,8.93;

Found:C,55.92;H,4.28;N,8.74%.

Example 55

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopentyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 252°C.

Analysis for $C_{23}H_{22}BrN_3O_2S$:

Calculated: C,57.03;H,4.58;N,8.67;

Found:C,56.87;H,4.66;N,8.68%.

Example 56

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 66 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 282°C.

Analysis for $C_{20}H_{19}N_3O_2S$ ($0.25H_2O$):

Calculated: C,64.93;H,5.31;N,11.36;

Found:C,64.84;H,5.28;N,10.81%.

Example 57

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 22 gave, after recrystallisation from acetone, the title compound as white crystals m.p. : 290-295°C.

Analysis for $C_{19}H_{17}N_3O_2S$:

Calculated: C,64.94;H,4.88;N,11.96;

Found: C, 64.81 ; H,4.95 ; N,11.68%.

Example 58

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 22 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 236-239°C.

Analysis for $C_{22}H_{23}N_3O_2S$:

Calculated: C,67.15;H,5.89;N,10.68;S,8.15;

Found:C,67.42;H,5.76;N,10.57;S,8.01%.

Example 59

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 28 gave, after recrystallisation from ether, the title compound as a white solid m.p. : 250°C.

Analysis for $C_{19}H_{17}N_3O_3$ ($0.5H_2O$):

Calculated: C,66.27;H,5.27;N,12.20;

Found:C,66.33;H,5.48;N,12.02%.

Example 60

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 29 gave, after recrystallisation from ethanol, the title compound as a cream powder m.p. : 303°C.

Analysis for $C_{20}H_{19}N_3O_3$ ($0.25H_2O$):

Calculated: C,67.88;H,5.55;N,11.87;

Found:C,67.90;H,5.50;N,11.98%.

Example 61

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 31 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. :>260°C.

Analysis for $C_{22}H_{21}N_3O_2$ (0.25 H_2O):

Calculated: C,72.61;H,5.95;N,11.55;

Found:C,72.73;H,5.96;N,11.59%.

Example 62

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 31 gave, after recrystallisation from the title compound as white crystals m.p. : 170°C.

Analysis for $C_{24}H_{25}N_3O_2$ (0.5H_2O):

Calculated: C,72.70;H,6.61;N,10.60;

Found:C,73.06;H,6.43;N,9.66%.

Example 63

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 31 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 194°C.

Analysis for $C_{25}H_{27}N_3O_2$ (0.5H_2O):

Calculated: C,73.15;H,6.87;N,10.24;

Found:C,73.01;H,6.84.N,10.26%.

Example 64

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 31 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 194°C.

Analysis for $C_{25}H_{25}N_3O_2$ (1.1H_2O):

Calculated: C,71.61;H,6.54;N,10.02;
Found:C,71.42.H,6.07;N,9.95%.

Example 65

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 33 gave, after recrystallisation from ethanol , the title compound as white crystals m.p. : >260°C.

Analysis for $C_{22}H_{21}N_3O_2$:
Calculated: C,73.52;H,5.89;N,11.69;
Found:C,73.60;H,5.97;N,11.66%.

Example 66

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-trifluoromethylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 35 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 155°C.

Analysis for $C_{25}H_{24}F_3N_3O_2$ ($0.5H_2O$):
Calculated: C,64.65;H,5.43;N,9.05;
Found:C,64.78;H,5.40;N,9.01%.

Example 67

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-trifluoromethoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 65 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 174-180°C.

Analysis for $C_{22}H_{18}F_3N_3O_3$ ($0.5H_2O$):
Calculated: C,60.27;H,4.37;N,9.58;
Found:C,60.24;H,4.28;N,9.50%.

Example 68

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-hydroxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 39 gave, after recrystallisation from methanol, the title compound as yellow crystals m.p. :179-180°C.

Analysis for $C_{21}H_{19}N_3O_3(1.25H_2O)$:

Calculated: C,65.70;H,5.64;N,10.94;

Found:C,65.46;H,5.45;N,10.92%.

Example 69

Cis-2,3,6,7,12,12a-hexahydro-6-(3-hydroxy-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 40 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. :320°C.

Analysis for $C_{22}H_{21}N_3O_4(0.25H_2O)$:

Calculated: C,66.74;H,5.47;N,10.61;

Found:C,66.72;H,5.46;N,10.53%.

Example 70

Cis-2,3,6,7,12,12a-hexahydro-6-(4-hydroxy-3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 41 gave, after recrystallisation from dichloromethane/ethanol, the title compound as yellow crystals m.p. :264-265°C.

Analysis for $C_{22}H_{21}N_3O_4$:

Calculated: C,67.51;H,5.41;N,10.74;

Found:C,67.05;H,5.41;N,10.62%.

Example 71

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-cyanophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 37 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p. : 246°C.

Analysis for $C_{25}H_{24}N_4O_2$ ($1H_2O$):
Calculated: C,69.75;H,6.09;N,13.01;
Found:C,69.50;H,5.96;N,12.86%.

Example 72
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from isopropylamine and the cis isomer of intermediate 42 gave, after recrystallisation from n-pentane, the title compound as white crystals m.p. : 130°C.
Analysis for $C_{25}H_{27}N_3O_2$ ($0.5H_2O$):
Calculated: C,73.15;H,6.87;N,10.24;
Found:C,73.39;H,7.08;N,9.81%.

Example 73
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from cyclopropylmethylamine and the cis isomer of intermediate 42 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 160°C.
Analysis for $C_{26}H_{27}N_3O_2$:
Calculated: C,75.52;H,6.58;N,10.16;
Found:C,75.54;H,6.62;N,10.08%.

Example 74
Cis-2,3,6,7,12,12a-hexahydro-6-(4-isopropylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from methylamine and intermediate 43 gave, after recrystallisation from ethanol, the title compound as white crystals m.p. : 244°C.
Analysis for $C_{24}H_{25}N_3O_2$:
Calculated: C,74.39;H,6.50;N,10.84;
Found:C,74.27;H,6.53;N,11.05%.

Example 75

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-nitrophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 45 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 182°C.

Analysis for $C_{24}H_{24}N_4O_4$ ($0.25H_2O$):

Calculated: C,65.97;H,5.65;N,12.82;

Found:C,65.92;H,5.62;N,12.96%.

Example 76

Cis-2,3,6,7,12,12a-hexahydro-6-(4-dimethylaminophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 47 gave after recrystallisation from methanol, the title compound as white crystals m.p. : 266°C.

Analysis for $C_{23}H_{24}N_4O_2$:

Calculated: C,71.11;H,6.23;N,14.42;

Found:C, 71.19 ; H, 6.24 ; N, 14.34%.

Example 77

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-pyridyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 48 gave after recrystallisation from chloroform, the title compound as white crystals m.p. : 312°C.

Analysis for $C_{20}H_{18}N_4O_2$:

Calculated: C,69.35;H,5.24;N,16.17;

Found:C,69.08;H,5.20;N,16.19%.

Example 78

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

a) To a stirred solution of intermediate 54 (0.5 g) and $NaHCO_3$ (0.14 g) in anhydrous $CHCl_3$ (20 mL) was added dropwise chloroacetyl chloride (0.27 mL) at 0°C. The resulting mixture was stirred for 1 hour at the same

temperature and diluted with $CHCl_3$ (20 mL). Water (10 mL) was then added dropwise with stirring to the mixture, followed by a saturated solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, (6R,12aR)-methyl 1,2,3,4-tetrahydro-2-chloroacetyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was obtained as an oil which was crystallised from ether to give a solid (0.38 g, m.p. : 233°C) which was used without further purification in the next step.

b) To a stirred suspension of the chloroacetyl intermediate (0.37 g) in MeOH (20 mL) was added at room temperature a solution of methylamine (33% in EtOH) (0.4 mL) and the resulting mixture was heated at 50°C under N_2 for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x20 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (99/1) and recrystallised from 2-propanol to give the title compound as white crystals (0.22 g) m.p. : 302-303°C.

Analysis for $C_{22}H_{19}N_3O_4$:
Calculated:C,67.86;H,4.92;N,10.79;
Found:C,67.77;H,4.92;N,10.74%.
$[\alpha]_D^{20°}$ = +71.0° (C=1.00; $CHCl_3$).

The following compounds were obtained in a similar manner:

Example 79
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione
The same two step procedure but starting from isopropylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 290-293°C.
Analysis for $C_{24}H_{23}N_3O_4$:
Calculated: C,69.05;H,5.55;N,10.07;
Found:C,69.06;H,5.49;N,10.12%.

$[\alpha]_D^{20°}$= +52.6° (C=1.14; $CHCl_3$).

Example 80

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from butylamine and intermediate 54 gave, after recrystallisation from toluene/hexane, the title compound as white crystals m.p. : 209-210°C.

Analysis for $C_{25}H_{25}N_3O_4$:

Calculated: C,69.59;H,5.84;N,9.74;

Found:C,69.70;H,5.93;N,9.74%.

$[\alpha]_D^{20°}$= +50.2° (C=0.53; $CHCl_3$).

Example 81

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isobutyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from isobutylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 227-228°C.

Analysis for $C_{25}H_{25}N_3O_4$:

Calculated: C,69.59;H,5.84;N,9.74;

Found:C,69.52;H,5.87;N,9.74%.

$[\alpha]_D^{20°}$= +45° (C=1.04; $CHCl_3$).

Example 82

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 54 gave, after recrystallisation from ether, the title compound as white crystals m.p. : 237-239°C.

Analysis for $C_{26}H_{25}N_3O_4$:

Calculated: C,70.41;H,5.68;N,9.47;

Found:C,70.13.H,5.67.N,9.42%.

$[\alpha]_D^{20°}$= +36.6° (C=0.98; $CHCl_3$).

Example 83

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-cyclohexylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclohexylmethylamine and the cis isomer of intermediate 56 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 209°C.

Analysis for $C_{28}H_{29}N_3O_4$:

Calculated: C,71.32;H,6.20;N,8.91;

Found:C,71.30;H,6.29;N,8.74%.

$[\alpha]_D^{20°}$= +40.0° (C=0.99; $CHCl_3$).

Example 84

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 57 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 204-205°C.

Analysis for $C_{25}H_{25}N_3O_3(0.5H_2O)$:

Calculated: C,70.74;H,6.17;N,9.90;

Found:C,70.98;H,6.09;N,9.92%.

$[\alpha]_D^{20°}$= +54.1° (C=1.03; $CHCl_3$).

Example 85

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from buylamine and intermediate 57 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 183-184°C.

Analysis for $C_{25}H_{27}N_3O_3(0.5H_2O)$:

Calculated: C,70.40;H,6.62;N,9.85;

Found:C,70.55;H,6.64;N,9.92%.

$[\alpha]_D^{20°}$ = +45.4° (C=1.04; $CHCl_3$).

Example 86

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 57 gave, after recrystallisation from ether, the title compound as white crystals m.p. : 210-211°C.

Analysis for $C_{26}H_{27}N_3O_3$:

Calculated: C,72.71;H,6.34;N,9.78;

Found:C,72.53;H,6.39;N,9.53%.

$[\alpha]_D^{20°}$ = +29.8° (C=1.07; $CHCl_3$).

Example 87

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 218-219°C.

Analysis for $C_{25}H_{24}ClN_3O_3$ (0.25 H_2O):

Calculated: C,66.08;H,5.43;N,9.25 ; Cl, 7.80;

Found: C, 66.11 ; H, 5.33 ; N, 9.03 ; Cl, 7.74%.

$[\alpha]_D^{20°}$ = +49.4° (C=1.03; $CHCl_3$).

Example 88

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 260-262°C.

Analysis for $C_{26}H_{26}ClN_3O_3$:

Calculated: C,67.31;H,5.65;Cl,7.64;N,9.06;

Found:C,66.98;H,5.67;Cl,8.06;N,9.04%.

$[\alpha]_D^{20°}$= +27.6° (C=1.05; $CHCl_3$).

Example 89

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 283-284°C.

Analysis for $C_{22}H_{20}ClN_3O_3$:

Calculated: C,64.47;H,4.92;Cl,8.65;N,10.25;

Found:C,64.49;H,4.92.Cl8.33.N,10.02%.

$[\alpha]_D^{20°}$= +61.3° (C=1.00; $CHCl_3$).

Example 90

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 302-304°C.

Analysis for $C_{24}H_{24}ClN_3O_3$:

Calculated: C,65.83;H,5.52;N,9.60;

Found:C,65.83;H,5.57.N,9.73%.

$[\alpha]_D^{20°}$= +39.8° (C=0.95; $CHCl_3$).

Example 91

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 61 gave, after recrystallisation from dichloromethane/methanol, the title compound as white crystals m.p. : 288-291°C.

Analysis for $C_{23}H_{21}N_3O_3$:

Calculated: C,71.30;H,5.46;N,10.85;

Found:C,71.27;H,5.49;N,10.96%.

$[\alpha]_D^{20°}$ = +65.6° (C=0.4; $CHCl_3$).

Example 92

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methylcyclopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylcyclopropylamine and intermediate 61 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 242-244°C.

Analysis for $C_{26}H_{25}N_3O_3$:

Calculated: C,73.05;H,5.89;N,9.83;

Found:C,72.90;H,5.93;N,9.98%.

$[\alpha]_D^{20°}$ = +55.4° (C=0.99; $CHCl_3$).

Example 93

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from methylamine and intermediate 63 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 262°C.

Analysis for $C_{24}H_{23}N_3O_2$:

Calculated: C,74.78;H,6.01;N,10.90;

Found:C,74.65;H,5.90;N,10.67%.

$[\alpha]_D^{20°}$ = +68.6° (C=0.98; $CHCl_3$).

Example 94

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 63 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 176°C.

Analysis for $C_{27}H_{27}N_3O_2$ ($0.25H_2O$):

Calculated: C,75.41 ; H, 6.45 ; N, 9.77;

Found:C, 75.25 ; H, 6.51 ; N, 9.75%.

$[\alpha]_D^{20°}$ = +57.9° (C=1.00; $CHCl_3$).

Example 95

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a stirred suspension of Intermediate 73 (12.5g) in MeOH (400ml) was added at room temperature a solution of methylamine (33% in EtOH) (13.7ml) and the resulting mixture was heated at 50°C under N_2 for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (1l). After washing with water (3 x 500ml), drying over Na_2SO_4 and evaporating to dryness, the white solid obtained was recrystallised from 2-propanol to give the title compound as white needles (7.5g).

mp : 298-300°C.

$[\alpha]_D^{20°}$ = + 71.3° (c = 0.55, $CHCl_3$).

Elemental analysis ($C_{22}H_{19}N_3O_4$) calculated: C, 67.86; H, 4.92; N, 10.79;
found: C, 67.79; H, 4.95; N, 10.61%.

Example 96

Cis-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure as used to prepare Example 1, but starting from methylamine and the cis isomer of Intermediate 74, gave after recrystallisation from ethanol, the title compound as white crystals m.p. : 275°C.

Analysis for $C_{23}H_{21}N_3O_4$ ($0.4H_2O$):

Calculated : C, 67.27 ; H, 5.35 ; N, 10.23;

Found : C, 67.36 ; H, 5.21 ; N, 10.31%.

Example 97

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure as used to prepare Example 78, but starting from veratrylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 224-226°C.

Analysis for $C_{30}H_{27}N_3O_6$:

Calculated : C,68.56 ; H,5.18 ; N,8.00;
Found : C,68.80 ; H,5.11 ; N,8.06%.
$[\alpha]_D^{20°}$ = + 43.9° (C = 1.02; $CHCl_3$).

Example 98
Cis-2,3,6,7,12,12a-hexahydro-6-(4-aminophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 75 (1.5 g) in methanol (100 mL) was added $SnCl_2.H_2O$ (3.06) and the resulting mixture was heated at reflux for 8 hours. The mixture was cooled to ambient temperature, poured into ice and was adjusted to pH5 with 1N NaOH. The methanol was evaporated off and the residue was basified to pH11 with 1N NaOH and extracted with EtOAc (2 x 150 mL). After drying over Na_2SO_4 and evaporation of EtOAc, the resulting yellow powder was purified by radial chromatography eluting with CH_2Cl_2 to give the title compound as a white powder (550 mg) m.p. : 192°C.
Analysis for $C_{24}H_{26}N_4O_2$ (1.3 H_2O):
Calculated : C,67.68 ; H,6.77 ; N, 13.15;
Found : C,67.74 ; H, 6.68 ; N, 13.02%.

Example 99
Cis-2,3,6,7,12,12a-hexahydro-6-(4-acetamidophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 98 (0.2 g) in THF (15 mL) was added triethylamine (76 µL) and acetyl chloride (39 µL) and the resulting solution was stirred at room temperature for 2 hours. After evaporation of THF, the resulting residue was taken up in CH_2Cl_2 (100 mL), washed with water (2 x 50 mL) and dried over Na_2SO_4. After evaporation of CH_2Cl_2, the resulting solid was recrystallised from MeOH/H_2O to give the title compound as a cream powder (120 mg) m.p. : 246°C.
Analysis for $C_{26}H_{28}N_4O_3$:
Calculated : C,70.25 ; H,6.35 ; N,12.60;
Found : C,69.85 ; H, 6.38 ; N,12.56%.

Example 100

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylsulfonamidophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 98 (0.2 g) in THF (5 mL) was added triethylamine (228 µL) and methanesulfonyl chloride (126 µL) and the solution was heated at reflux for 6 hours. After evaporation of THF, the residue was taken up in CH_2Cl_2, washed with water and dried over Na_2SO_4. After evaporation of CH_2Cl_2, the residue was purified by radial chromatography eluting with CH_2Cl_2/MeOH (95/5) to give the title compound as a brown powder (30 mg) m.p. : 188°C.

Analysis for $C_{25}H_{28}N_4O_4S$ (0.75 H_2O):

Calculated : C,60.77 ; H,6.02 ; N,11.34;

Found : C,60.61 ; H, 6.02 ; N,10.82%.